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(57) Abstract

Disclosed are compounds which inhibit β-amyloid peptide release and/or its synthesis, and, accordingly, have utility in treating Alzheimer's disease. Also disclosed are pharmaceutical compositions comprising a compound which inhibits β-amyloid peptide release and/or its synthesis as well as methods for treating Alzheimer's disease both prophylactically and therapeutically with such pharmaceutical compositions.

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CYCLOALKYL, LACTAM, LACTONE AND RELATED COMPOUNDS, PHARMACEUTICAL COMPOSITIONS COMPRISING SAME, AND METHODS FOR INHIBITING β-AMYLOID PEPTIDE RELEASE AND/OR ITS SYNTHESIS BY USE OF SUCH COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/064,851 which was converted pursuant to 37 C.F.R. § 1.53(b)(2)(ii) from U.S. Patent Application No. 08/780,025, filed December 23, 1996.

Field of the Invention

This invention relates to compounds which inhibit β-amyloid peptide release and/or its synthesis, and, accordingly, have utility in treating Alzheimer's disease.

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All of the above publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

State of the Art

Alzheimer's Disease (AD) is a degenerative brain disorder characterized clinically by progressive loss of memory, cognition, reasoning, judgment and emotional stability that gradually leads to profound mental deterioration and ultimately death. AD is a very common cause of progressive mental failure (dementia) in aged humans and is believed to represent the fourth most common medical cause of death in the United States. AD has been observed in races and ethnic groups worldwide and presents a major present and future public health problem. The disease is currently estimated to affect about two to three million individuals in the United States alone. AD is at present incurable. No treatment that effectively prevents AD or reverses its symptoms and course is currently known.

The brains of individuals with AD exhibit characteristic lesions termed senile (or amyloid) plaques, amyloid angiopathy (amyloid deposits in blood vessels) and neurofibrillary tangles. Large numbers of these lesions, particularly amyloid plaques and neurofibrillary tangles, are generally found in several areas of the human brain important for memory and cognitive function in patients with AD. Smaller numbers of these lesions in a more restrictive anatomical distribution are also found in the brains of most aged humans who do not have clinical AD. Amyloid plaques and amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome) and Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type

(HCHWA-D). At present, a definitive diagnosis of AD usually requires observing the aforementioned lesions in the brain tissue of patients who have died with the disease or, rarely, in small biopsied samples of brain tissue taken during an invasive neurosurgical procedure.

The principal chemical constituent of the amyloid plaques and vascular amyloid deposits (amyloid angiopathy) characteristic of AD and the other disorders mentioned above is an approximately 4.2 kilodalton (kD) protein of about 39-43 amino acids designated the β-amyloid peptide (βAP) or sometimes Aβ, AβP or β/A4. β-Amyloid peptide was first purified and a partial amino acid sequence was provided by Glenner, et al.[1] The isolation procedure and the sequence data for the first 28 amino acids are described in U.S. Patent No. 4,666,829[2].

Molecular biological and protein chemical analyses have shown that the β-amyloid peptide is a small fragment of a much larger precursor protein termed the amyloid precursor protein (APP), that is normally produced by cells in many tissues of various animals, including humans. Knowledge of the structure of the gene encoding APP has demonstrated that β-amyloid peptide arises as a peptide fragment that is cleaved from APP by protease enzyme(s). The precise biochemical mechanism by which the β-amyloid peptide fragment is cleaved from APP and subsequently deposited as amyloid plaques in the cerebral tissue and in the walls of the cerebral and meningeal blood vessels is currently unknown.

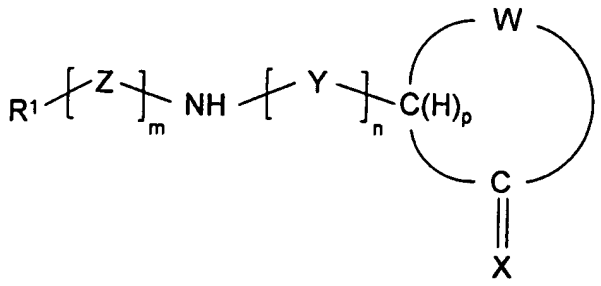
Several lines of evidence indicate that progressive cerebral deposition of β-amyloid peptide plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe[3]. The most important line of evidence is the discovery that missense DNA mutations at amino acid 717 of the 770-amino acid isoform of APP can be found in affected members but not unaffected members of several families with

a genetically determined (familial) form of AD (Goate, et al.[4]; Chartier Harlan, et al.[5]; and Murrell, et al.[6]) and is referred to as the Swedish variant. A double mutation changing lysine^{595}-methionine^{596} to asparagine^{595}-leucine^{596} (with reference to the 695 isoform) found in a Swedish family was reported in 1992 (Mullan, et al.[7]). Genetic linkage analyses have demonstrated that these mutations, as well as certain other mutations in the APP gene, are the specific molecular cause of AD in the affected members of such families. In addition, a mutation at amino acid 693 of the 770-amino acid isoform of APP has been identified as the cause of the β-amyloid peptide deposition disease, HCHWA-D, and a change from alanine to glycine at amino acid 692 appears to cause a phenotype that resembles AD is some patients but HCHWA-D in others. The discovery of these and other mutations in APP in genetically based cases of AD prove that alteration of APP and subsequent deposition of its β-amyloid peptide fragment can cause AD.

Despite the progress which has been made in understanding the underlying mechanisms of AD and other β-amyloid peptide related diseases, there remains a need to develop methods and compositions for treatment of the disease(s). Ideally, the treatment methods would advantageously be based on drugs which are capable of inhibiting β-amyloid peptide release and/or its synthesis *in vivo*.

SUMMARY OF THE INVENTION

This invention is directed to the discovery of a class of compounds which inhibit β-amyloid peptide release and/or its synthesis and, therefore, are useful in the prevention of AD in patients susceptible to AD and/or in the treatment of patients with AD in order to inhibit further deterioration in their condition. The class of compounds having the described properties are defined by formula I below:



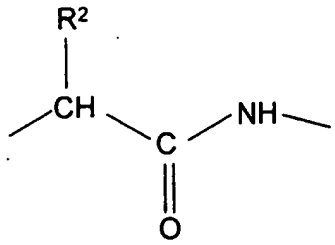
I

wherein R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

W, together with $-C(H)_pC(=X)-$, forms a cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein each of said cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures are optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, $-NHC(O)R^4$, $-NHSO_2R^4$, $-C(O)NH_2$, $-C(O)NHR^4$, $-C(O)NR^4R^4$, $-S(O)R^4$, $-S(O)_2R^4$, $-S(O)_2NHR^4$ and $-S(O)_2NR^4R^4$ where each R^4 is independently selected from the group consisting of alkyl, substituted alkyl, or aryl;

X is selected from the group consisting of oxo (=O), thiooxo (=S), hydroxyl (-H, -OH), thiol (H,-SH) and hydro (H,H);

Y is represented by the formula:



wherein each R^2 is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

Z is represented by the formula -T-CX′X″C(O)- where T is selected from the group consisting of a bond covalently linking R^1 to -CX′X″-, oxygen, sulfur, -NR^5 where R^5 is hydrogen, acyl, alkyl, aryl or heteroaryl group;

X′ is hydrogen, hydroxy or fluoro,

X″ is hydrogen, hydroxy or fluoro, or X′ and X″ together form an oxo group;

m is an integer equal to 0 or 1;

n is an integer equal to 0, 1 or 2;

p is an integer equal to 0 or 1 such that when *p* is zero, the ring defined by W and -$C(H)_pC(=X)$- is unsaturated at the carbon atom of ring attachment to Y and when *p* is one, the ring is saturated at the carbon atom of ring attachment to Y,

with the following provisos:

A. when R^1 is 3,5-difluorophenyl, R^2 is -CH_3, Z is -$CH_2C(O)$-, *m* is 1, *n* is 1, and *p* is 1, then W, together with >CH and >C=X, does not form a 2-(S)-indanol group;

B. when R^1 is phenyl, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with >CH and >C=X, does not form a trans-2-hydroxy-cyclohex-1-yl group;

C. when R^1 is phenyl, Z is $-CH_2C(O)-$, *m* is 1, *n* is 0, and *p* is 1, then W, together with >CH and >C=X, does not form a gamma-butyrolactone group or a 5,5-dimethyl-gamma-butyrolactone group;

D. when R^1 is phenyl, Z is $-CH_2C(O)-$, *m* is 1, *n* is 0, and *p* is 1, then W, together with >CH and >C=X, does not form a ϵ-caprolactam group;

E. when R^1 is cyclopropyl, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with >CH and >C=X, does not form an N-methylcaprolactam group;

F. when R^1 is 4-chlorobenzoyl-CH_2-, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with >CH and >C=X, does not form an 2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one;

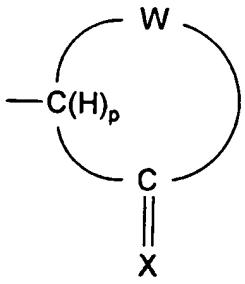
G. when R^1 is 2-phenylphenyl, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with >CH and >C=X, does not form an 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one;

H. when R^1 is $CH_3OC(O)CH_2-$, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with >CH and >C=X, does not form an 2,3-dihydro-1-(*t*-butylC(O)CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

I. when R^1 is 4-ethoxyphenyl, 2,4,6-trimethylphenyl, 4-phenylphenyl, $CH_3OC(O)CH_2-$, 4-$HOCH_2$-phenyl, 2,4,6-trifluorophenyl, 2-trifluoromethyl-4-fluorophenyl, or CH_3S-, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with >CH and >C=X, does not form a 2,3-dihydro-1-(*N,N*-diethylamino-CH_2CH^2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

J. when R^1 is 2,6-difluorophenyl, R^2 is $-CH_3$, Z is $-CH(OH)C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with >CH and >C=X, does not form a 2,3-dihydro-1-(*N,N*-diethylamino-CH_2CH^2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one,

K. when *m* is 1 and *n* is 1, then



does not equal cycloalkyl of from 3 to 8 carbon atoms optionally substituted with 1 to 3 alkyl groups.

Accordingly, in one of its method aspects, this invention is directed to a method for inhibiting β-amyloid peptide release and/or its synthesis in a cell which method comprises administering to such a cell an amount of a compound or a mixture of compounds of formula I above effective in inhibiting the cellular release and/or synthesis of β-amyloid peptide.

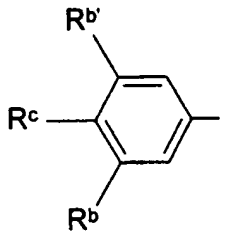
Because the *in vivo* generation of β-amyloid peptide is associated with the pathogenesis of AD[8,9], the compounds of formula I can also be employed in conjunction with a pharmaceutical composition to prophylactically and/or therapeutically prevent and/or treat AD. Accordingly, in another of its method aspects, this invention is directed to a prophylactic method for preventing the onset of AD in a patient at risk for developing AD which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula I above.

In yet another of its method aspects, this invention is directed to a therapeutic method for treating a patient with AD in order to inhibit further deterioration in the condition of that patient which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula I above.

In formula I above, when *m* is zero (i.e., there is a covalent bond from R^1 to NH), R^1 is preferably aryl (including substituted aryl) or heteroaryl (including substituted heteroaryl). In this embodiment, further preferred R^1 groups include

(a) phenyl,

(b) a substituted phenyl group of the formula:



wherein R^c is selected from the group consisting of acyl, alkyl, alkoxy, alkylalkoxy, azido, cyano, halo, hydrogen, nitro, trihalomethyl, thioalkoxy, and wherein R^b and R^c are fused to form a heteroaryl or heterocyclic ring with the phenyl ring wherein the heteroaryl or heterocyclic ring contains from 3 to 8 atoms of which from 1 to 3 are heteroatoms independently selected from the group consisting of oxygen, nitrogen and sulfur

R^b and $R^{b'}$ are independently selected from the group consisting of hydrogen, halo, nitro, cyano, trihalomethyl, alkoxy, and thioalkoxy with the proviso that when R^c is hydrogen, then R^b and $R^{b'}$ are either both hydrogen or both substituents other than hydrogen,

(c) 2-naphthyl,

(d) 2-naphthyl substituted at the 4, 5, 6, 7 and/or 8 positions with 1 to 5 substituents selected from the group consisting alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, thioalkoxy, aryl, and heteroaryl,

(e) heteroaryl, and

(f) substituted heteroaryl containing 1 to 3 substituents selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, cyano, halo, nitro, heteroaryl, thioalkoxy, thioaryloxy provided that said substituents are not *ortho* to the heteroaryl attachment to the -NH group.

When *m* is zero, particularly preferred substituted phenyl R^1 groups include mono-, di- and tri-substituted phenyl groups including 3,5-disubstituted phenyls such as 3,5-dichlorophenyl, 3,5-difluorophenyl, 3,5-di(trifluoromethyl)-phenyl, etc.; 3,4-disubstituted phenyls such as 3,4-dichlorophenyl, 3,4-difluorophenyl, 3-(trifluoromethyl)-4-chlorophenyl, 3-chloro-4-cyanophenyl, 3-chloro-4-iodophenyl, 3,4-methylenedioxyphenyl, etc.; 4-substituted phenyls such as 4-azidophenyl, 4-bromophenyl, 4-chlorophenyl, 4-cyanophenyl, 4-ethylphenyl, 4-fluorophenyl, 4-iodophenyl, 4-(phenylcarbonyl)phenyl, 4-(1-ethoxy)ethylphenyl, etc., 3,4,5-trisubsituted phenyls such as 3,4,5-trifluorophenyl, 3,4,5-trichlorophenyl, etc.

Specific R^1 groups for when *m* is zero include 3,4-dichlorophenyl, 4-phenylfurazan-3-yl, and the like.

When *m* is zero, other preferred R^1 substituents include, by way of example, 2-naphthyl, quinolin-3-yl, 2-methylquinolin-6-yl, benzothiazol-6-yl, 5-indolyl, phenyl, and the like.

When *m* is one, preferred R^1 groups include unsubstituted aryl groups such as phenyl, 1-naphthyl, 2-naphthyl, etc.; substituted aryl groups such as monosubstituted phenyls (preferably substituents at 3 or 5 positions); disubstituted phenyls (preferably substituents at 3 and 5 positions); and

trisubstituted phenyls (preferably substituents at the 3,4,5 positions). Preferably, the substituted phenyl groups do not include more than 3 substituents. Examples of substituted phenyls include, for instance, 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-nitrophenyl, 2-methylphenyl, 2-methoxyphenyl, 2-phenoxyphenyl, 2-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-butoxyphenyl, 4-*iso*-propylphenyl, 4-phenoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxymethylphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 3-nitrophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-phenoxyphenyl, 3-thiomethoxyphenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-dimethoxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-di-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4,5-trifluorophenyl, 3,4,5-trimethoxyphenyl, 3,4,5-tri-(trifluoromethyl)phenyl, 2,4,6-trifluorophenyl, 2,4,6-trimethylphenyl, 2,4,6-tri-(trifluoromethyl)phenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,5-difluorophenyl, 2-fluoro-3-trifluoromethylphenyl, 4-fluoro-2-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 4-benzyloxyphenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-chlorophenyl, 2,3,4,5,6-pentafluorophenyl, 2,5-dimethylphenyl, 4-phenylphenyl, 2-fluoro-3-trifluoromethylphenyl,

When *m* is one, other preferred R^1 groups include, by way of example, adamantyl, benzyl, 2-phenylethyl, 3-phenyl-*n*-propyl, 4-phenyl-*n*-butyl, methyl, ethyl, *n*-propyl, *iso*-propyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-valeryl, *n*-hexyl, cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopent-1-enyl, cyclopent-2-enyl, cyclohex-1-enyl, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl, $-CH_2$-cyclohexyl, $-CH_2$-cyclopentyl, $-CH_2CH_2$-cyclopropyl, $-CH_2CH_2$-cyclobutyl,

-CH_2CH_2-cyclohexyl, -CH_2CH_2-cyclopentyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, fluoropyridyls (including 5-fluoropyrid-3-yl), chloropyridyls (including 5-chloropyrid-3-yl), thien-2-yl, thien-3-yl, benzothiazol-4-yl, 2-phenylbenzoxazol-5-yl, furan-2-yl, benzofuran-2-yl, thionaphthen-2-yl, thionaphthen-3-yl, thionaphthen-4-yl, 2-chlorothiophen-5-yl, 3-methylisoxazol-5-yl, 2-(thiophenyl)thien-5-yl, 6-methoxythionaphthen-2-yl, 3-phenyl-1,2,4-thiooxadiazol-5-yl, 2-phenyloxazol-4-yl, indol-3-yl, 1-phenyl-tetraol-5-yl, allyl, 2-(cyclohexyl)ethyl, $(CH_3)_2CH=CHCH_2CH_2CH(CH_3)$-, $\phi C(O)CH_2$-, thien-2-yl-methyl, 2-(thien-2-yl)ethyl, 3-(thien-2-yl)-*n*-propyl, 2-(4-nitrophenyl)ethyl, 2-(4-methoxyphenyl)ethyl, norboran-2-yl, (4-methoxyphenyl)methyl, (2-methoxyphenyl)methyl, (3-methoxyphenyl)methyl, (3-hydroxyphenyl)methyl, (4-hydroxyphenyl)methyl, (4-methoxyphenyl)methyl, (4-methylphenyl)methyl, (4-fluorophenyl)methyl, (4-fluorophenoxy)methyl, (2,4-dichlorophenoxy)ethyl, (4-chlorophenyl)methyl, (2-chlorophenyl)methyl, (1-phenyl)ethyl, (1-(*p*-chlorophenyl)ethyl, (1-trifluoromethyl)ethyl, (4-methoxyphenyl)ethyl, $CH_3OC(O)CH_2$-, benzylthiomethyl, 5-(methoxycarbonyl)-*n*-pentyl, 3-(methoxycarbonyl)-*n*-propyl, indan-2-yl, (2-methylbenzofuran-3-yl), methoxymethyl, $CH_3CH=CH$-, $CH_3CH_2CH=CH$-, (4-chlorophenyl)$C(O)CH_2$-, (4-fluorophenyl)$C(O)CH_2$-, (4-methoxyphenyl)$C(O)CH_2$-, 4-(fluorophenyl)-$NHC(O)CH_2$-, 1-phenyl-*n*-butyl, $(\phi)_2CHNHC(O)CH_2CH_2$-, $(CH_3)_2NC(O)CH_2$-, $(\phi)_2CHNHC(O)CH_2CH_2$-, methylcarbonylmethyl, (2,4-dimethylphenyl)$C(O)CH_2$-, 4-methoxyphenyl-$C(O)CH_2$-, phenyl-$C(O)CH_2$-, $CH_3C(O)N(\phi)$-, ethenyl, methylthiomethyl, $(CH_3)_3CNHC(O)CH_2$-, 4-fluorophenyl-$C(O)CH_2$-, diphenylmethyl, phenoxymethyl, 3,4-methylenedioxyphenyl-CH_2-, benzo[b]thiophen-3-yl, $(CH_3)_3COC(O)NHCH_2$-, *trans*-styryl, $H_2NC(O)CH_2CH_2$-, 2-trifluoromethylphenyl-$C(O)CH_2$, $\phi C(O)NHCH(\phi)CH_2$-, mesityl, $CH_3CH(=NHOH)CH_2$-, 4-CH_3-ϕ-$NHC(O)CH_2CH_2$-, $\phi C(O)CH(\phi)CH_2$-, $(CH_3)_2CHC(O)NHCH(\phi)$-, $CH_3CH_2OCH_2$-, $CH_3OC(O)CH(CH_3)(CH_2)_3$-, 2,2,2-trifluoroethyl, 1-(trifluoromethyl)ethyl, 2-CH_3-benzofuran-3-yl, 2-(2,4-dichlorophenoxy)ethyl, ϕSO_2CH_2-, 3-cyclohexyl-*n*-propyl, $CF_3CH_2CH_2CH_2$- and N-pyrrolidinyl.

Still other preferred R^1 groups include those set forth in the Tables below.

When *n* is one or two, each R^2 is preferably (and independently for *n* = 2) selected from the group consisting of alkyl, substituted alkyl, alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclic.

Particularly preferred R^2 substituents include, by way of example, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, $-CH_2CH(CH_2CH_3)_2$, 2-methyl-*n*-butyl, 6-fluoro-*n*-hexyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, *iso*-but-2-enyl, 3-methylpentyl, $-CH_2$-cyclopropyl, $-CH_2$-cyclohexyl, $-CH_2CH_2$-cyclopropyl, $-CH_2CH_2$-cyclohexyl, $-CH_2$-indol-3-yl, *p*-(phenyl)phenyl, *o*-fluorophenyl, *m*-fluorophenyl, *p*-fluorophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl, *p*-nitrobenzyl, *m*-trifluoromethylphenyl, *p*-$(CH_3)_2NCH_2CH_2CH_2O$-benzyl, *p*-$(CH_3)_3COC(O)CH_2O$-benzyl, *p*-$(HOOCCH_2O)$-benzyl, 2-aminopyrid-6-yl, *p*-(N-morpholino-CH_2CH_2O)-benzyl, $-CH_2CH_2C(O)NH_2$, $-CH_2$-imidazol-4-yl, $-CH_2$-(3-tetrahydrofuranyl), $-CH_2$-thiophen-2-yl, $-CH_2$(1-methyl)cyclopropyl, $-CH_2$-thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, $-CH_2$-C(O)O-*t*-butyl, $-CH_2$-$C(CH_3)_3$, $-CH_2CH(CH_2CH_3)_2$, -2-methylcyclopentyl, -cyclohex-2-enyl, $-CH[CH(CH_3)_2]COOCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2C(CH_3)=CH_2$, $-CH_2CH=CHCH_3$ (cis and trans), $-CH_2OH$, $-CH(OH)CH_3$, $-CH(O$-*t*-butyl$)CH_3$, $-CH_2OCH_3$, $-(CH_2)_4NH$-Boc, $-(CH_2)_4NH_2$, $-CH_2$-pyridyl (e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl), $-CH_2$-naphthyl (e.g., 1-naphthyl and 2-naphthyl), $-CH_2$-(N-morpholino), *p*-(N-morpholino-CH_2CH_2O)-benzyl, benzo[b]thiophen-2-yl, 5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl, 6-methoxynaphth-2-yl, $-CH_2CH_2SCH_3$, thien-2-yl, thien-3-yl, and the like.

Compounds of this invention include, by way of example,

1-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-aminodibenzosuberane

1-(R)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino-2-(S)-indanol

1-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino-2-(R)-indanol

1-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino-2-indanol

2-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino-1-cyclohexanol

1-(R,S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino-1,2,3,4-tetrahydro-2-naphthol

1-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-aminobenz[f]cycloheptan-2-ol

5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-5,7-dihydro-6H-dibenzo[a,c]cyclohepten-6-ol

1-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-aminoindan-2-one

2-(N'-(phenylacetyl)-L-alaninyl)aminocyclohexan-1-one

5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-5,7-dihydro-6H-dibenzo[a,c]cyclohepten-6-one

3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino-γ-butyrolactone

3-(N'-(3,4-dichlorophenyl)-L-alaninyl)amino-γ-butyrolactone

4-(N'-(cyclopentylacetyl)-L-alaninyl)amino-1,1-dimethyl-3-isochromanone

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1,1-dimethyl-3-isochromanone

3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-γ-butyrolactam

3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-δ-valerolactam

1-benzyl-3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino-δ-valerolactam

3-N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-4-methyl-ϵ-caprolactam

3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1,2,3,4-tetrahydroquinolin-2-one

1-benzyl-3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1,2,3,4-tetrahydroquinolin-2-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1,2,3,4-tetrahydroisoquinolin-3-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-2-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-methyl-1,2,3,4-tetrahydroisoquinolin-3-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-6-fluoro-1,2,3,4-tetrahydroisoquinolin-3-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-7-fluoro-1,2,3,4-tetrahydroisoquinolin-3-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-2-phenethyl-1,2,3,4-tetrahydroisoquinolin-3-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-2-methyl-1,2,3,4-tetrahydroisoquinolin-3-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-6-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-7-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one

(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-(9-aminofluroren-1-yl)glycine δ-lactam

3-(N'-(phenylacetyl)-L-alaninyl)amino-ϵ-caprolactam

3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino-ϵ-caprolactam

3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-benzyl-ϵ-caprolactam

3-(S)-N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-(2-methoxyethyl)-ϵ-caprolactam

3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-ethyl-ϵ-caprolactam

3-N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-ethyl-ϵ-caprolactam

3-N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-ethyl-ϵ-caprolactam

3-N'-(3,5-difluorophenylacetyl)-L-alaninyl-amino)-7-benzyl-ϵ-caprolactam

3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-benzyl-4,7-methano-ϵ-caprolactam

3-(S)-(N'-(cyclopentylacetyl)-L-alaninyl)amino-1-benzyl-ϵ-caprolactam

3-(S)-(N'-(cyclopentylacetyl)-L-phenylglycinyl)amino-1-benzyl-ϵ-caprolactam

3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-(2-phenethyl)-ϵ-caprolactam

3-(S)-(N'-(cyclopentylacetyl)-L-phenylglycinyl)amino-1-(2-phenethyl)-ϵ-caprolactam

3-(N'-(3,4-dichlorophenyl)-D,L-alaninyl)amino-ϵ-caprolactam

3-(S)-(N'-(cyclopropylacetyl)-L-phenylglycinyl)amino-1-methyl-ϵ-caprolactam

3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-8-octanelactam

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-7-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-(pyrid-2-yl)-1,2,3,4-tetrahydroisoquinolin-3-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-(pyrid-3-yl)-1,2,3,4-tetrahydroisoquinolin-3-one

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-(pyrid-4-yl)-1,2,3,4-tetrahydroisoquinolin-3-one

3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]-amino-1-methyl-2-indolinone

3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-methyl-4-phenyl-3,4-*trans*-dihydrocarbostyril

3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-methyl-4-phenyl-3,4-*cis*-dihydrocarbostyril

3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-4-phenyl-3,4-*trans*-dihydrocarbostyril

1-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

1-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-3-ethyl-4'-fluoro-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

3-(3,5-difluorophenylacetyl)amino-1-ethyl-5,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-benzyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

3-(N'-(cyclopentylacetyl)amino-1-ethyl-5,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

3-(3,5-difluorophenylacetyl)amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-methyl-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-ethyl-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-methyl-5-thia-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

5-{N'-(3,5-difluorophenylacetyl)-L-alaninyl}-amino-3,3-dimethyl-5,7-dihydro-6H-benz[b]azepin-6-one

5-{N'-(3,5-difluorophenylacetyl)-L-alaninyl}amino-3,3,7-trimethyl-5,7-dihydro-6H-benz[b]azepin-6-one

5-{N'-[(S)-3,5-difluoromandelyl]-L-alaninyl}amino-3,3,7-trimethyl-5,7-dihydro-6H-benz[b]azepin-6-one

1-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-ethyl-5,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

5-(S)-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-(S)-[N'-((S) and (R)-3,5-difluorophenyl-α-hydroxyacetyl)-L-alaninyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-(S)-[N'-(3,5-difluorophenyl-α-ketoacetyl)-L-alaninyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-(S)-[N'-(3,5-difluorophenylacetyl)-L-valinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-(S)-[N'-(3,5-difluorophenylacetyl)-L-*tert*-leucinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-(S)-[N'-((S)-3,5-difluorophenyl-α-hydroxyacetyl)-L-valinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-(S)-[N'-((S)-3,5-difluorophenyl-α-hydroxyacetyl)-L-*tert*-leucinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-7-(methoxyacetyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-7-(methylcarboxylate)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-7-(3,3-dimethyl-2-butanoyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-7-(morpholinylacetyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-(S)-(N'-((S)-(+)-2-Hydroxy-3-methylbutyryl)-L-alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-[N'-cyclopentyl-α-hydroxyacetyl)-L-valinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-(S)-(N'-((S) and (R)-3,3-dimethyl-2-hydroxybutyryl)-L-alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-[N'-cyclopentyl-α-hydroxyacetyl)-L-*tert*-leucinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-[N'-cyclopentyl-α-hydroxyacetyl)-L-alaninyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-5,7-dihydro-6H,7H-dibenz[b,d]azepin-6-one

5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-[N'-(2-hydroxy-3-methylbutyryl)-L-valinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-(S)-[N'-((S and R)-2-hydroxy-3,3-dimethylbutyryl)-L-valinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-(4-phenyl-furazan-3-yl)alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-(3,5-difluorophenylacetyl)-L-alaninyl}amino-7-methyl-1,2,3,4,5,7-hexahydro-6H-dicyclohexyl[b,d]azepin-6-one

5-{N'-(3,5-difluorophenylacetyl)-L-alaninyl}amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-(3,5-difluorophenylacetyl)-L-alaninyl}amino-7-cyclopropymethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-(3,5-difluorophenylacetyl)-L-alaninyl}amino-7-(2',2',2'-trifluoroethyl)-5,7-dihydro-H-dibenz[b,d]azepin-6-one

5-{N'-(3,5-difluorophenylacetyl)-L-alaninyl}amino-7-cyclohexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-[(S)-3,5-difluoromandelyl]-L-alaninyl}amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-[(S)-3,5-difluoromandelyl]-L-alaninyl}-amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-[(S)-3,5-difluoromandelyl]-L-alaninyl}amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-[(S)-3,5-difluoromandelyl]-L-alaninyl}amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-[(S)-3,5-difluoromandelyl]-L-alaninyl}amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-[(S)-3,5-difluoromandelyl]-L-valinyl}amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-[(S)-3,5-difluoromandelyl]-L-valinyl}amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-[(S)-3,5-difluoromandelyl]-L-valinyl}amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-[(S)-3,5-difluoromandelyl]-L-valinyl}amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-[(S)-3,5-difluoromandelyl]-L-valinyl}amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5-{N'-[(S)-3,5-difluoromandelyl]-L-valinyl}amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

3-(N'-(3,4-methylenedioxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(2-methoxyphenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(4-isopropylphenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(ethoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(4-phenoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(4-ethoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(2,5-dimethoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(3,5-difluorobenzoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(o-tolylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(3,3-diphenylpropionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(3-phenoxypropionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(indole-3-acetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(4-(trifluoromethyl)phenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-((4-methylphenoxy)acetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(4-(hydroxymethyl)phenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(2-phenoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

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(74) Agents: SWISS, Gerald, F. et al.; Burns, Doane, Swecker & Mathis, L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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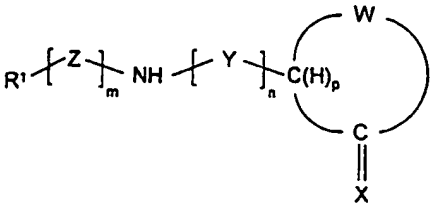

(I)

(57) Abstract

Disclosed are compounds for Formula (I) wherein the substituents are as defined in the claims which inhibit β-amyloid peptide release and/or its synthesis, and, accordingly, have utility in treating Alzheimer's disease. Also disclosed are pharmaceutical compositions comprising a compound which inhibits β-amyloid peptide release and/or its synthesis as well as methods for treating Alzheimer's disease both prophylactically and therapeutically with such pharmaceutical compositions.

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INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/[redacted]97/22986

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D243/16 C07D243/24 C07D401/04 C07D223/18 A61K31/55
C07D409/12 C07D407/12 C07D401/14 C07D409/14 C07D217/24
C07D223/10 C07D225/02 C07D211/76 C07D207/273 C07D311/76

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 97 30072 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA)) 21 August 1997 see page 5, line 4 - page 5, line 7; claims 1,29,30 ---	32-90
Y	EP 0 652 009 A (ELI LILLY AND COMPANY & ATHENA NEUROSCIENCES, INC.) 10 May 1995 see page 3, line 23 - page 3, line 30; claims 1,3 ---	32-90
A	EP 0 677 517 A (ELI LILLY AND COMPANY) 18 October 1995 see claims 1,8 ---	32-90
A	WO 95 25118 A (TRUSTEES OF TUFTS UNIVERSITY) 21 September 1995 see claim 1 --- -/--	32-90

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 June 1998	10.07.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herz, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter[redacted] Application No
PCT[redacted]97/22986

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D307/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 278 335 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 13 February 1976 * Examples * see claims 1-4 -----	32,34, 35,40, 41,43, 45,46, 61,63, 65,69, 70,72, 74,75

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
8 June 1998	10.07.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herz, C

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/22986

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-31
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 1 to 31 are directed to a therapeutical method performed on humans. Under the terms of Rule 39.1 (iv) PCT, the International Searching Authority is not required to carry a search on such claims.

2. [X] Claims Nos.: 32-90(part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 32-90(part)

The definition of substituents R(1) and W is too general and/or encompasses too broad a range of totally different chemical entities, only partly supported by examples given in the descriptive part of the application. The vast number of theoretically conceivable compounds resulting from the combination of all claimed substituents precludes a comprehensive search. Also, in view of the large number of compounds, which are defined by the general definition in the independent claims, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application. (see Guidelines, Chapter III, paragraph 2.3).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/[redacted]97/22986

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INTERNATIONAL SEARCH REPORT

[redacted]nation on patent family members

Interna[redacted] Application No
PCT/[redacted]97/22986

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